Glycaemic Control and Cardiovascular Risk Factors in Type 2 Diabetes: a Population-based Study

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The objective of this study was to estimate the prevalence of poor glycaemic control and cardiovascular risk factors in an Italian population-based cohort of subjects with Type 2 diabetes mellitus (DM). Out of a cohort of 1967 subjects (estimated completeness of ascertainment 80 %), 1574 (80 %) were investigated, and adherence to targets for control of the European NIDDM Policy Group assessed. Prevalence of poor glycemic control (HbA_{1c} > = 8) was 47.7 %. Obesity was present in 23.4 % of the cohort, hypertension in 83.4 %, hypertriglyceridaemia (>2.26 mM) in 19.3 %, hypercholesterolaemia (>6.46 mM) in 25.5 %, and low HDL-cholesterol (<0.90 mM in men and <1.03 mM in women) in 13.7 %. Only 153 (9.7 %) subjects were free from other disorders. Subjects were treated as follows: 26.2 % exclusively by general practitioners; 13.3 %, 69.9 %, 10.9 %, and 5.9 % with diet, oral hypoglycaemic drugs, insulin, and both, respectively. Multiple linear regression analysis showed associations between HbA_{1c} and fibrinogen ($p < 0.001$), total cholesterol ($p = 0.006$), and triglycerides ($p = 0.04$), independent of age, sex, duration of diabetes, and antidiabetic treatment. Neither BMI nor blood pressure were associated with HbA_{1c}. In conclusion, this Italian population-based cohort of subjects with Type 2 DM showed a high prevalence of poor glycaemic control, high consumption of oral hypoglycaemic drugs, and an independent association between glycaemic control and cardiovascular risk factors (fibrinogen, total cholesterol, and triglycerides). The presence of obesity or hypertension was not significantly associated with glycaemic control. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Most data in subjects with Type 2 diabetes mellitus (DM), suggest that poor glycaemic control is associated with increased vascular complications and premature mortality.[1–3] There are only limited data on the degree of glycaemic control in population-based cohorts of subjects with Type 2 DM and on associated risk factors for vascular disease.[4,5] Furthermore, the pattern of antidiabetic treatment varies widely across different countries,[5–7] depending more on the prescribing attitude of general practitioners and diabetologists than on cost/benefit differences between treatments.

In Northern Italy, we have previously identified a population-based cohort of subjects with Type 2 DM with high estimated completeness of ascertainment.[8] That cohort was the study base for the present report, in which we evaluated adherence to targets for control suggested by the European NIDDM Policy Group.[9]

Subjects and Methods

The study base for this report were all 1967 subjects with known Type 2 diabetes on the prevalence date (1 October 1988) identified in a survey conducted in Casale Monferrato, Northern Italy.[8] Multiple incomplete sources of ascertainment were employed (diabetic clinic, general practitioners, prescriptions, hospital discharges and diabetic devices), obtaining a high estimated completeness of ascertainment (80 %).[10] Out of 1967 patients, 515 (26.2 %) were exclusively cared for by general practitioners. In 1991–92, 1574 subjects of the cohort (80 %) were reinvestigated. Of the remaining, 280 had died (160 women and 120 men), 7 had migrated from the area and 106 could not be located. At the time of the cohort identification (1 October 1988), subjects recruited for this study exhibited both a slightly lower duration of diabetes (8.2 ± 6.6 yr vs 9.5 ± 8.2 yr, $p < 0.001$) and frequency of hypertension (WHO criteria, 47.7 % vs 51.0 %, $p < 0.001$) than those not included. The study design has been described in detail elsewhere.[11] In brief, patients were invited (by telephone) to be examined at the diabetic clinic or at home. All patients providing informed consent were interviewed and examined by

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three of us, after training to ensure standardized data collection and blood pressure measurement. Height and weight were measured in indoor clothing without shoes with a beam balance and a stadiometer, and body mass index (BMI) was calculated. Obesity was defined as BMI >30 kg m^{-2}. Blood pressure was measured with mercury sphygmomanometers to the nearest 2 mmHg in the right arm, at the start of examination, in a sitting position, three consecutive times after an initial 5-min rest. Reported values are the average of the second and the third readings (phase 1 for systolic and phase 5 for diastolic pressure). Hypertension was defined as systolic blood pressure $>=140$ mmHg and/or diastolic blood pressure $>=90$ mmHg or treatment with antihypertensive drugs.[12] Venous blood samples were collected after a 12 h fast for determinations of plasma glucose, triglycerides, total cholesterol (enzymatic-colorimetric methods), HDL-cholesterol (enzymatic-colorimetric method, after precipitation with Mn^{2+}), fibrinogen (Clauss method),[13] and haemoglobin A_{1c} (HbA_{1c}) (HPLC, Daiichi, Menarini, Japan, laboratory reference range 3.8–5.5 %). All plasma and urine determinations were performed in a single centralized laboratory. Hypertriglyceridaemia was defined as values >2.26 mM, hypercholesterolaemia as values >6.46 mM, low HDL-cholesterol as values <0.90 mM in men and <1.03 in women, and good glycaemic control as values of HbA_{1c} within three standard deviations (SD) above the upper limit of the reference range (8.0 %), in accordance with European Consensus.[9]

Statistical Analysis

Triglyceride values were non-normally distributed and were analysed after logarithmic transformation. Student's unpaired *t*-test, variance analysis, and chi-squared test were performed to compare means for continuous variables or percentage for discrete variables. Means are expressed $\pm$ standard deviation (SD). Multiple linear regression analysis was performed with HbA_{1c} as dependent variable and age, sex, duration of diabetes, plasma glucose, total cholesterol, HDL-cholesterol, log-triglycerides, fibrinogen, hypertensive status, BMI, and antidiabetic treatment as covariates. Two-way interaction terms which were *a priori* biologically plausible were tested, that is, age with antidiabetic treatment, duration with antidiabetic treatment, and BMI with antidiabetic treatment. Interactions that were statistically significant were retained in the model. Results of multiple linear regression analysis are shown as the regression coefficient (b values; the estimated difference in HbA_{1c} levels as a result of a unit increase in the independent variable) and *p* values of the regression coefficient. Analyses were performed with the SAS statistical software.[14]

Results

The percentage of subjects treated with diet, oral hypoglycemic drugs, insulin and both insulin and oral agents were 13.3 %, 69.9 %, 10.9 %, and 5.9 %, respectively. Duration of diabetes in subjects treated with diet, oral drugs, insulin or both, were, respectively, 8.9 ± 5.1 yr, 10.9 ± 6.6 yr, 15.3 ± 8.5 yr, and 15.9 ± 7.5 yr ($p < 0.001$). No significant differences in age across class of antidiabetic treatment were found (mean age in the whole cohort 68.6 ± 11.2 yr).

Figure 1 shows HbA_{1c} levels in the cohort. In 696 (44.2 %) subjects, poor glycaemic control was found (HbA_{1c} $>=8.0$ %). Table 1 shows adherence to targets for control suggested by the European NIDDM Policy Group. The prevalence of obesity, hypertension, hypercholesterolaemia, hypertriglyceridaemia, and low HDL-cholesterol were, respectively, 23.4 %, 83.4 %, 25.5 %, 19.3 %, and 13.7 %. Only 153 (9.7 %) diabetic subjects were free of other disorders.

Multiple linear regression analysis was then performed to assess variables associated with HbA_{1c}, independently of age, sex, duration of diabetes, and antidiabetic treatment. Data on all variables were available for 1503 patients. HbA_{1c} level was significantly associated with plasma glucose (b=0.0009, $p<0.001$), total cholesterol (b=0.00008, p=0.006), log-triglycerides (b=0.005, p=0.04) and fibrinogen (b=0.00002, $p<0.001$). This model explained 32 % of the variability in HbA_{1c} levels. Adding hypertensive status, HDL-cholesterol, and BMI to previous independent variables did not significantly modify the estimates of the variables. Two-way interaction terms were not significant.

Conclusions

The main finding of this population-based study of Type 2 diabetes was the high prevalence of poor glycaemic control (44 %), defined as values higher than 3 SD above the upper limit of the reference range, in accordance with the European consensus recommendations.[9] Most of diabetic subjects recruited in this study were elderly and compliance to insulin treatment may be low in this age group. However, even in the elderly, poor glycemic control has been found to predict coronary heart disease.[2] In comparison with the United Stated and Northern Europe, we found only 15 % of subjects were insulin-treated (either insulin alone or in combination with oral

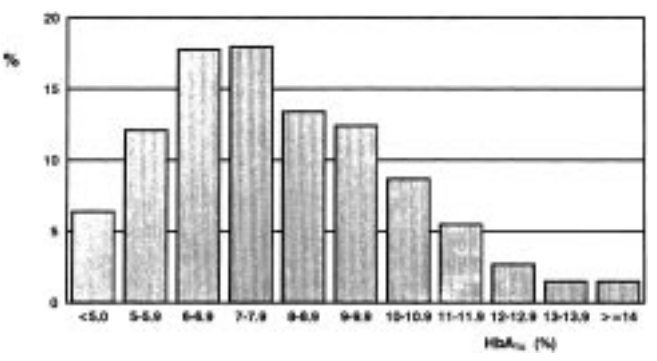

Figure 1. HbA_{1c} levels in the population-based cohort of Type 2 diabetes of Casale Monferrato (Italy)

Table 1. Adherence to targets for control suggested by the European NIDDM Policy Group in an Italian population-based cohort of patients with Type 2 diabetes

	Men (n = 688)		Women (n = 886)		p
	Prevalence	(%)	Prevalence	(%)	
Fasting glucose >7.8 mM	387	(56.2)	527	(59.5)	ns
$HbA_{1c} \geq 8$ %	287	(41.7)	409	(46.2)	ns
BMI >30 kg m^{-2}	130	(18.9)	239	(27.0)	<0.001
Total cholesterol >6.5 mM	128	(18.6)	273	(30.8)	<0.001
HDL-cholesterol <0.9 mM in men <1.0 mM in women	70	(10.2)	196	(22.1)	<0.001
Triglycerides >2.2 mM	119	(17.3%)	185	(20.9)	0.06
Hypertension	537	(78.1)	776	(87.6)	<0.001

agents). Since we found also a lower prevalence of obesity, a low frequency of diagnosis of secondary failure to oral agents could contribute to the lower employment of insulin treatment in this cohort.

This is the first European study which provides data on both glycaemic control and cardiovascular risk factors in a population-based cohort of patients with Type 2 diabetes. Studies done on selected groups of patients who attend diabetic clinics are generally biased, because these groups are not representative of the overall diabetic population. For example, one study done in Casale Monferrato found that general practitioners selectively referred younger patients and those with worse values of fasting plasma glucose to the diabetic clinic.[7] To identify the present cohort, multiple sources of ascertainment were employed and estimated completeness of ascertainment was high, using capture–recapture methods (80 %).[10] Subjects not recruited were probably a subgroup of those exclusively cared for by general practitioners, and slightly lower prevalence of poor blood glucose in these subjects is likely.

In multiple linear regression analysis, with HbA_{1c} as the dependent variable, after adjustment for sex, age, duration of diabetes, and antidiabetic treatment, we found that fibrinogen, total cholesterol and triglycerides were independently associated with HbA_{1c}. This finding—although derived from a cross-sectional study—provided additional evidence of the negative impact of poor glycaemic control on associated cardiovascular risk factors. Recently, the potential role of fibrinogen in macrovascular complications of Type 2 diabetes has gained considerable interest;[15] the correlation between HbA_{1c} and fibrinogen has been attributed to decreased insulin concentration or action.[16]

In accordance with a previous study,[4] we found no association of obesity, hypertensive status or HDL-cholesterol with HbA_{1c}. In contrast with studies performed in other countries, we found that almost 75 % of diabetic subjects were cared for by the diabetic clinic. This finding has been reported also in other Italian surveys and is probably due to the presence of the public diabetic clinics in the Italian National Health Service.

Finally, we confirmed that in subjects with Type 2 DM, obesity, hypertension, and dyslipidaemia are frequently associated in a plurimetabolic syndrome; only in 10 % of diabetic subjects was no other disorder found.

In conclusion, this population-based cohort of people with Type 2 DM showed a high prevalence of poor glycaemic control and an independent association between glycaemic control and the cardiovascular risk factors fibrinogen, total cholesterol, and triglycerides. The presence of obesity or hypertension was not associated with significant changes in glycaemic control.

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